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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,009	02/01/2002	Michelle Schaffer	P1869R1	2130

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,009	SCHAFFER ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *6-8,28-34,36,37,39-48 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-5,9-27,35,38 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/1/02, 7/11/03,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, 9-27, 35, 38, and 49, drawn to IGF-1 crystal and method of making, classified in class 530, subclass 300.

II. Claims 6-8, drawn to a method of treating a mammal by administering effective amount, classified in class 514, subclass 2.

III. Claims 28-34, drawn to method of identifying indirect agonists, classified in class 436, subclass 86.

IV. Claim 36, drawn to a method of determining the three dimensional structure of IGF-1, classified in class 436, subclass 86.

V. Claim 37, drawn to machine-readable data storage, classified in class 369.

VI. Claims 39-42 and 50, drawn to of using the three-dimensional structure of IGF-1 in a method to identify compound that bind to IGF-1 binding region, classified in class 702, subclass 19.

VII. Claims 43-47, drawn to of designing compound that mimic the 3-dimenssional surface structure of IGF-1, classified in class 702, subclass 19.

VIII. Claim 48, drawn to a chemical compound identified by a method involving three-dimensional structure of IGF-1, Classification is unknown because the applicant does not claim a compound with specific chemical structure.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the crystal can be used in a method to determine the three dimensional structure of GF-1.

Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the method of Group III does not utilize the crystal of Group I.

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the

process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the structure of IGF-1 can be determined by NMR spectroscopy, whereas the crystal can be used in a pharmaceutical composition for treatment of diseases.

Inventions I and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not disclosed as capable to use together.

Inventions I and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the crystal can be used in a method to purify the IGF-1 protein or in a Pharmaceutical composition to treat diseases.

Inventions I and VII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the crystal can be used in a method to purify the IGF-1 protein or in a Pharmaceutical composition to treat diseases.

Inventions I and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the two inventions are distinct chemical entities.

Inventions II, III, IV, VI, and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are independent methods having different steps and different product.

Inventions II and those of V and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are not used together. The method of invention II does not utilize the machine-readable data storage or the compound of invention VIII.

The methods of inventions III, VI, and VII and the machine-readable data storage of invention V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the machine-readable data storage can be utilized in different method to design agonist or antagonist or construct a three dimensional model of IGF-1 or homologous proteins.

Inventions IV and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are not used together. The method of invention IV does not utilize the machine-readable data storage.

Inventions III, IV, and VI and that of VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are not used together. The methods of inventions III and VI do not utilize the compound of VIII.

Inventions V and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are not used together.

Inventions VII and VIII are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the compound of VIII can be identified by different methods such as screening assay.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ginger R. Dreger on March 9, 2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5, 9-27, 35, 38, and 49. Affirmation of this election must be made by applicant in replying to this Office action. Claims 6-8, 28-34, 36, 37, 39-48, and 50 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-5, 9-27, 35, 38, and 49 are under consideration.

The disclosure is objected to because of the following informalities: The specification contains reference to specific amino acid residues without identifying the amino acid sequence(s) with a sequence identification number.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 9-27, 35, 38, and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 9-27, 35, 38, and 49 are directed to all possible crystals of any IGF-1 and compositions comprising said crystal, a cocrystalline IGF-1 with N,N-bis-(3-D-gluconamidopropyl)-deoxycholamine, any IGF-1 crystal which produces the atomic coordinate shown in appendix 1, and any heavy metal derivative of any IGF-1 crystal. The specification, however, only provides a single representative species of these crystals encompassed by these claims. The specification teaches the crystallization of human IGF-1 of SEQ ID NO: 1 in orthorhombic crystal having the space Group $C222_1$ with cell unit dimension a = 31.831 Å, b = 71.055 Å, and c = 65.995 Å; and $\alpha = \beta = \gamma = 90°$. There is no disclosure of any particular teaching on how to change the crystallization conditions to obtain any IGF-1 protein crystal with the change in the protein sequence, or any other crystal form. There is no disclosure of any heavy metal derivative of any crystal, let alone an isomorophous crystal. The specification also fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the cell dimension recited in claim 2, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. The insertion of SEQ ID NO: 1 in claim 2 would obviate this rejection with regard to claim 2.

Similarly claims 9 and 10 are directed to a method of crystallizing any IGF-1 protein under any crystallization conditions. Claims 11-26 are included with this rejection because they are dependent from claim 9 and do not identify the IGF-1 protein by specific sequence identification number or the exact crystallization conditions. The specification, however, only provides a single representative species of this method encompassed by these claims. The specification teaches the crystallization of human IGF-1 of SEQ ID NO: 1 in orthorhombic crystal having the space Group $C222_1$ with cell unit dimension a = 31.831 Å, b = 71.055 Å, and c = 65.995 Å; and $\alpha = \beta = \gamma = 90°$ under the conditions described in the specification, see the paragraph bridging pages 18 and 19. There is no disclosure of any particular teaching on how to change the crystallization conditions to obtain any IGF-1 protein crystal with the change in the protein sequence, or any other crystal form. The specification also fails to describe additional representative species of these methods by any identifying structural

characteristics or properties other than the conditions recited in claim 26, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-5, 9-27, 35, 38, and 49 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the orthorhombic crystal of human IGF-1 of SEQ ID NO: 1 having the space Group $C222_1$ with cell unit dimension a = 31.831 Å, b = 71.055 Å, and c = 65.995 Å; and $\alpha = \beta = \gamma = 90°$ crystallized under the conditions described in the specification, see the paragraph bridging pages 18 and 19. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all possible crystals of IGF-1 proteins, which formed under any crystallization conditions. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any crystal of IGF-1 protein having any amino acid sequence and a method of making said crystal under any conditions or any polyethylene glycol as a precipitant. The specification provides guidance and examples in the form of an assay to obtain, presumably, the IGF-1 protein of SEQ ID NO: 1, crystallize the protein under the conditions described on page 26, first paragraph, (example 1) and characterize the IGF-1 crystal, presumably, of SEQ ID NO: 1 (example 1). While molecular biological techniques and genetic manipulation to make any IGF-1 protein having any amino acid sequence are known in the prior art and the skill of the artisan are well developed, knowledge regarding the crystallization conditions to obtain a suitable crystal for structure determination by the X-ray diffraction method is lacking. Thus, searching a crystallization conditions for any IGF-1 protein is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a crystallization conditions is enormous. Applicants should be reminded that growing protein crystals to a suitable size that diffracts X-ray is not amenable to scientific investigation. It relies mostly on trial and error. A minor a change in an amino acid sequence such as a conservative mutation may have a profound effect on the crytallizability of a protein under a given crystallization conditions. In many instants, a crystal can be obtained, but it diffracts X-ray poorly. The formation of IGF-1 crystal complex with an agent that binds to IGF-1 is highly unpredictable. There are two known methods for obtaining a crystal complex with a heavy metal or a compound that bind to

the protein. The first is to include in the crystallization conditions a heavy metal or a compound that binds to IGF-1. In many instants, the compound-IGF-1 complex crystal may not form and would require new screening for crystallization conditions, which would produce a crystal suitable for X-ray diffraction. Also, the crystal may not be isomorphous to the underivatized crystal. The second method is socking underivatized crystals in the mother liquor from which the crystal has grown containing the desired ligand. Once again, that may lead to the destruction of the crystal or recrystallization of the protein. Since routine experimentation in the art does not include screening vast numbers of crystallization condition which may include going out to space to attempt growing crystals in microgravity environment where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact crystallization conditions and the amino acid sequence which is being crystallized. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-5, 9-27, 35, 38 and 49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) Claims 1, 5, 9, 27, 35, 38 and 49 contain the undefined abbreviation and/or acronym IGF-1. Abbreviations and acronyms must be defined at least once in the claims.

(b) The phrase "crystal with the structure coordinates shown in Appendix 1" in claim 38 renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The atomic coordinate in Appendix 1 describes the structure of the IGF-1 protein of, presumably, SEQ ID NO: 1, and not the orthorhombic crystal having the space Group $C222_1$ with cell unit dimension a = 31.831 Å, b = 71.055 Å, and c = 65.995 Å; and $\alpha = \beta = \gamma = 90°$. For examination purposes only, the phrase is assumed to mean "whose X-ray diffraction pattern is consistent with a three dimensional structure of IGF-1 protein defined by the atomic coordinates of Appendix 1.

(c) Claims 2-4, and 10-26 are included in this rejection because they are dependent on rejected claims and do not correct the deficiencies of the claim from which they depend.

The claims are free of prior art.

Claims directed to a specific crystal comprising SEQ ID NO: 1 and a specific method of making said crystal would be considered favorably.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1652